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HYPERTHERMIA IN THE TREATMENT OF CANCER

N. M. BLEEHEN

From the University Department and Medical Research Council Unit of Clinical Oncology and Radiotherapeutics, The Medical School, Cambridge CB2 2QH

Summary.—The clinical use of hyperthermia for the treatment of cancer continues to be hampered by technical difficulties. Current methods of local heating do not give satisfactory heat profiles. The biological concepts behind the potentially successful use of this treatment modality are discussed together with a review of the advantages and disadvantages of the various techniques employed. Some clinical studies using microwaves and radiofrequency heating are reviewed.

HYPERTHERMIA has been revived as a cancer treatment following much experimental work over the past decade. Clinical hyperthermia is usually carried out at temperatures of 40–45°C. The methodologies still are inadequate and results largely anecdotal. Even so, well documented tumour responses have been demonstrated in a large number of patients with advanced disease. Recent reviews of the history and clinical data (Har Kedar & Bleehen, 1976), biological aspects (Feld & Bleehen, 1979) and heating techniques (Hand & ter Haar, 1981) provide comprehensive summaries of much of the relevant data. Recent symposia also contain numerous relevant publications (Proceedings of the International Symposium on Cancer Therapy by Hyperthermia and Radiation, 1975; Cancer Therapy by Hyperthermia and Radiation, 1978; Conference on Hyperthermia in Cancer Treatment, 1979; Proceedings of 3rd International Symposium on Hyperthermia, 1980). Detailed references to work cited in this paper will be found in these publications and in other contributions to this symposium. This review presents a short summary of some of the relevant biological and physical aspects, together with a few details of clinical studies.

BIOLOGY

Experimental effects may be considered for heat alone or in combination with radiation and drugs. Brief details are given below but detailed references are given in the reviews cited, and in particular, in Field & Bleehen, 1979.

Heat alone

Studies with several different *in vitro* cell lines of both animal and human origin have defined various responses to heat, usually in the range 39–46°C. The effect on surviving fraction is related both to the magnitude of the temperature and to the duration of exposure. An initial shoulder on the survival curve is followed by an exponential slope. The size of the shoulder is reduced and the slope of the exponential part of the curve increases rapidly with increasing temperatures. Considerable quantitative differences exist between cell lines but initial suggestions that malignant cells were more heat-sensitive than normal ones are probably incorrect. There is also no consistent difference between the heat response of hypoxic and oxic cells provided that their pH is maintained at around 7·2. However, there are now numerous data which demonstrate enhanced thermal sensitivity of cells at a low pH, such as might be expected inside tumours. In contrast to X-rays, cells in S phase are sensitive to heat.

The response of tumour cells *in vitro* is matched by those *in vivo*, but local environmental changes become of importance in terms of pH, hypoxia, blood flow and temperature gradients. Of obvious concern is the effect on normal tissues, as they will also respond to hyperthermic stimuli and express damage. This may be less than in a tumour because of advantageous conditions of vas-

cularity, oxygenation and pH, but the qualitative response is similar.

Heat-induced thermal resistance to a second heat shock may be induced either by fractionated treatments at the same temperature or by a preliminary pre-heat period at a lower temperature. Implications of this for clinical therapy relate to tolerance which might be induced by a slow build-up of heat during the treatment period and also the frequency with which treatments may be given.

Various mechanisms for cell killing by heat have been proposed and include direct damage of DNA, membrane damage at the cell surface and lysosomes, induction of special proteins and physiological effects such as collapse of the tumour microvasculature.

Heat with radiation

Heat and X-radiation have been shown to interact synergistically. There may be by several mechanisms manifested by a reduction in the potential for accumulation and repair of sublethal X-ray damage and recovery from potentially lethal damage. Current experimental data support the view that similar combined effects are seen in tumours and normal tissues but the time course of recovery from heat damage is different. Experimental tumours recover more slowly than normal tissue with greater therapeutic gain when heat follows the irradiation by several hours.

These observations suggest a strategy for clinical therapy in which doses of X-rays are followed about 4 h later by hyperthermia, which should then act preferentially on residual hypoxic cells but not interact excessively in normal tissues. Such a concept assumes that tumour and surrounding normal tissue temperatures will be similar, but it must be remembered that blood cooling of normal tissues may also enhance therapeutic gain by reason of a temperature differential.

Heat with drugs

Hyperthermia has been shown to interact with many drugs. These include alkylating agents and nitrosoureas, where increased drug activation and target interaction are the probable mechanisms; antitumour antibiotics such as bleomycin, where heat inhibition of recovery from potentially lethal damage occurs; or adriamycin, where increased drug access is induced. Principal clinical interest relates to the alkylating agents, particularly for perfusion techniques. Enhanced effects on normal tissues such as bone marrow render the use with systemic hyperthermia more problematical, but trials are in progress.

HYPERTHERMIA TECHNIQUES

Numerous methods have been described for inducing local or whole-body hyperthermia. These are summarized here and presented in greater detail in the references listed in the introduction. It is fair to say that no method currently available permits an accuracy or versatility of treatment comparable with that possible with the ionizing radiations used in radiotherapy. Precision in delivery of radiation dose is possible in the latter because of predictable physical characteristics; variability of heat levels is not only due to imperfections in the technology but also to local physiological variables, such as blood flow.

Whole body

Although the radiations which are the subject of this meeting are only incidental to whole-body and perfusion techniques, mention must be made of them in this context. Uniformly raising the core temperature of the patient up to around a maximum of 42°C for periods of several hours will not only affect the primary tumour, but also any metastases. However, systemic toxicity, particularly if cytotoxic drugs are used as well, may be limiting; temperature boosting at specific sites by additional localized heating techniques might then be advantageous. There still remains the risk that impaired heat exchange in normal tissues could increase normal tissue effects.

Whole-body heating has been achieved by a variety of methods. Those involving heat exchange from outside include wax-bath immersion (Pettigrew *et al.*, 1974), heated suits (Bull *et al.*, 1979) or blankets (Larkin, 1979) and radiant-heat cabinets boosted with RF (Pomp, 1978). Heat exchange of perfused blood is also being used (Parks *et al.*, 1979). The results of 588 patients, collected from the literature, with a variety of late-stage disease, indicate a 31% tumour response rate of which 6% are complete responders. These patients, treated either by heat alone or in combination with chemotherapy, have how-

ever usually only shown rather transient responses which have not been maintained.

Regional perfusion

Isolated regional perfusion has been used to treat more localized tumours, particularly sarcomas and melanomas of limbs, either alone or in combination with drugs (Stehlin *et al.*, 1979). Favourable results have been claimed in 856 patients collected from 9 series reported to date. Assessment of these reports is however difficult in the absence of suitable controls.

Intracavitary

Intracavitary infusion has been used to heat the bladder (Ludgate *et al.*, 1976), with disappointing results due to excessive damage to normal tissue. Peritoneal lavage has also been used in a very limited number of patients for widespread intra-abdominal malignancy (Spratt *et al.*, 1980).

RF and microwaves

The majority of work on clinical hyperthermia employs local heating methods using RF, microwaves or ultrasound (reviewed by Hand & ter Haar, 1981). These have the advantages of being relatively non-invasive to the patient, apart from thermometry and interstitial techniques. Energy deposition is only limited by the power output of the equipment, and heat dissipation by the tumour and normal tissues perfused with blood at near-normal temperature. However, there are major limitations in their use resulting from the nature of the physical and biological interactions of these radiations with the various tissues encountered, which result in considerable non-uniformity of temperature and difficulties in heating tumours at depth. Additionally, RF and microwaves interact with the materials of most temperature measuring devices, usually necessitating measurement whilst heating power is transiently switched off. Newer devices with suitable dielectric constants are being developed which should overcome this problem but are currently still much larger than desirable.

Microwave heating has been the most frequently used method. Frequencies commonly used have been 433, 915 and 2450 MHz because of availability. Surface treatments are simple and numerous types of waveguide applicators, sometimes with skin cooling, have been designed. Penetration is lost at frequencies below 1000 MHz and development of multi-applicator and phased array systems can increase the useful depth and precision of localization. Coaxial applicators and interstitial implantable guides have also been described for specialized applications but thermal gradients are considerable.

RF heating (0·5–30 MHz) also has many advocates. In particular, at the higher frequencies, inductive coupling methods may successfully heat deeper tissues. There still remain problems with excessive heating in fat, rather inadequate localization and variability of temperature profile.

Ultrasound

Focused ultrasound is being developed following reported successes with superficial ultrasound. This has the advantage of not interacting with thermometry devices, and has good penetration in soft tissues but requires a coupling medium. There is unwanted disturbance in penetration due to gas or bone which severely restricts its use for most thoracic and many abdominal tumours.

CLINICAL PRACTICE

Requirements

It is necessary with currently available methods to consider the use of different techniques for tumours at different sites. Most will be able to heat superficially placed tumours (up to about 2 cm deep). However, this is not the major clinical problem, which is that of deep-seated tumours nearer the mid-longitudinal axis of the body. Reliable and uniform heating at such depths has not yet been substantially documented.

Before considering some specific clinical examples of the use of microwave and RF methods, it is important to define some of the requirements that clinicians expect. Not all of these are essential but most will need satisfying before the present usage in pilot studies can be expanded into routine clinical practice.

Physical requirements of the system should include reliability of the equipment which preferably should be as simple

as possible so that technicians can operate it. Reproducibility of power output is important with the possibility of heating at depth, together with surface cooling when required. It should be possible to localize the treatment volume and achieve reasonable homogeneity of temperature. It should be possible to define the minimum tumour and maximum normal-tissue temperatures. Physically acceptable thermometry techniques which are also not too difficult to insert at appropriate sites are essential. It is to be hoped that non-invasive temperature measurement will become possible in future. The heating time should also be of an acceptable duration, without too long a build-up period during which both unnecessary discomfort to the patient and thermal tolerance might result.

Microwave and radiofrequency heating

It is not profitable to review the results of all published clinical series, as almost all demonstrate the possibility of producing regressions with single or fractionated heat treatments (periods of 15 min to 2 h at 41–50°C). Choice of temperature, time and homogeneity of heating depend on many factors including tumour site, type of equipment and whether or not treatment is being combined with radiotherapy or chemotherapy. With care it is also accepted that these regressions may occur in the absence of significant normal-tissue damage, especially if skin-cooling is employed. Responses vary from complete, with durations of several months or years, to partial responses of only a few weeks; some do not respond at all. No clear histological pattern emerges for thermal sensitivity.

Controlled trials to assess the enhancement of radiation or chemotherapy by heat are few but tend to confirm the laboratory data. Kim & Hahn (1979) reported on the results of 27·12 MHz heating of superficial tumours to 41–43·5°C for 30–90-min sessions and radiation therapy. Both conventionally radio-resistant and radiosensitive tumours were included. Of patients receiving radiation alone, there were 12/49 (26%) complete responders (CR). When other lesions in the same patients were treated with heat and radiation, 42/54 (78%) showed a complete response. Enhanced skin reactions only occurred in areas where there was previous scarring, skin-grafting or when fractionated doses in excess of 5 Gy per session were used. These reactions occurred when heat was applied before radiation. U *et al.* (1980), using 915 and 2450 MHz in a similar but smaller study, reported complete responders for radiation alone, heat alone and radiation plus heat of 1/7, 0/6 and 6/7 respectively.

Another randomized study is that by Arcangeli *et al.* (1980), which includes multiple daily fraction-radiation therapy, 500 MHz hyperthermia and chemotherapy, for the treatment of malignant nodes in the neck. Overall response rates at the end of treatment were 20/25 for radiotherapy (12/25 CR), 21/22 for radiotherapy and heat (17/22 CR), 20/21 for heat plus adriamycin or bleomycin (9/21 CR), and 10/22 for drugs alone (3/11 CR). Numbers are small but the differences between the drugs alone and when combined with heat are significant ($P < 0{\cdot}01$).

Most data reported so far have employed conventional applicator designs. New techniques are now being reported which claim better localization of heat at depth. Storm *et al.* (1979) have described annular RF applicators (13·56 MHz) which have been used to treat both superficial and deep tumours and report responses in many tumour types, including those in the abdomen and chest. Le Veen *et al.* (1976) using a similar frequency, also claim tumour destruction at depth. Turner (1981) has discussed the theoretical basis for a variable-frequency microwave phased array system. At 70 MHz he demonstrates theoretical evidence for good heating at depth which should be useful for treatment of thoracic and abdominal tumours. Commercial equipment based on this concept is now under trial.

CONCLUSIONS

Hyperthermia is a treatment modality now based on a considerable amount of good experimental data. Current evidence suggests that under appropriate conditions it should be useful as an adjunct to conventional therapy. Evidence for its value as a unique treatment is less convincing. It is likely, however, that with better technical design of heat delivery and temperature measurement, and possibly with modifications of blood perfusion and the biochemical milieu of the tumour which improve the selectivity for tumour tissue, even this may be achieved. Current clinical results are still only preliminary and must be assessed in the light of the late stage of the disease selected. As with other treatment modalities, more favourable selection of tumours should ultimately improve results if techniques can be improved to justify it.

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